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FROMMER LAWRENCE & HAUG
745 FIFTH AVENUE- 10TH FL.
NEW YORK, NY 10151

EXAMINER	
HUYNH, PHUONG N	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/763,362	BODMER ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/16/08; 1/16/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,8,18,29-33,35 and 36* is/are pending in the application.

4a) Of the above claim(s) *18, 30, 32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,8,29,31,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-2, 8, 18, 29-33, 35 and 36 are pending.

2. Applicant's election with traverse of species, Claims 1-2, 8, 18, 29, 31, 35 and 36 (now claims 1-2, 8, 29, 31, 35 and 36) drawn to a conjugate comprising a first sequence and a second sequence, wherein the first sequence comprises an antibody or antibody fragment which binds to an antigen presenting cell (APC), and wherein the second sequence comprises a Notch ligand or a fragment thereof, wherein the second sequence comprises a Notch ligand DSL domain and at least one EGF-like repeat, and wherein the second sequence retains Notch signaling activity that read on the species of antibody or antibody fragment which binds to CD206 as the antigen presenting cell (APC) surface molecule and human Delta1 DSL as the Notch ligand sequence and at least one EGF-like repeat as the second sequence, filed Oct 16, 2008 is acknowledged.

The traversal is on the grounds that claim 1 is generic to all species of APC surface molecules, Notch ligand DSL domains, and EGF-like repeats. Applicants understand that, upon the allowance of a generic claim, claims to additional species will be considered, as provided by 37 C.F.R. § 1.141. Applicants also understand that the Examiner can broaden the search to include other species, *e.g.,* upon determining that a species is allowable, or when there is a relationship among the species and/or number of species is not too great.

As a traverse, Applicants point to MPEP Section 803 which states that a requirement for election is inappropriate when the generic claim includes sufficiently few species that a search and examination of all the species at one time would not impose a serious burden on the examiner. For the present application, the number of APC surface molecules, Notch ligand DSL domains, and EGF-like repeats to be searched is low. For instance, claim 35 recites only fourteen APC surface molecules, and claim 36 recites only twelve Notch ligands. Thus, the Applicant respectfully requests the Examiner to withdrawal the election of species, or at least permit more than one APC surface molecule, Notch ligand DSL domain, and EGF-like repeat.

As stated in the restriction mailed April 17, 2008, there is an examination and search burden for these patentably distinct species of conjugate comprising distinct targeting antibody or antibody fragment that binds to different antigen on the surface of APC such as the ones recited in claim 35 or any antibody or antibody fragment binds to any antigen presenting cell (APC)

linked to different Notch ligand such as the ones recited in claim 36 due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different sequences such as the ones recited in claim 36, classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Upon allowance of the generic claim, applicants will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. However, no generic claims are allowable at this time.

3. Claims 18, 30, 32 and 33 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-2, 8, 29, 31, 35 and 36 drawn to a conjugate comprising a first sequence and a second sequence, wherein the first sequence comprises an antibody or antibody fragment which binds to an antigen presenting cell (APC), and wherein the second sequence comprises a Notch ligand or a fragment thereof, wherein the second sequence comprises a Notch ligand DSL domain and at least one EGF-like repeat, and wherein the second sequence retains Notch signaling activity that read on the species of the first sequence comprising antibody or antibody fragment that binds to CD206 as the antigen presenting cell surface molecule and the species of second sequence comprising a human Delta1 as the Notch ligand are being acted upon in this Office Action.

5. In view of the amendment filed October 16, 2008 and January 16, 2008, the following rejections remain.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2, 8, 29, and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a conjugate comprising an antibody or antigen

binding fragment thereof which binds to an APC surface molecule selected from the group consisting of CD205 (DEC205), CD204, CD 14, CD206, TLR, Langerin (CD207), DC-SIGN (CD209), CD32, CD68, CD83, CD33, CD54, BDCA-2, BDCA-3, BDCA-4 wherein the antibody or binding fragment thereof is conjugated to a human Notch ligand selected from the group consisting of human Delta1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, a human Notch ligand fragment selected from the group consisting of the amino acid sequence of SEQ ID NO: 25, SEQ ID NO: 29, SEQ ID NO: 32, SEQ ID NO: 36, SEQ ID NO: 38 and SEQ ID NO: 39 wherein the fragment retains Notch signaling activity; (2) a fusion protein comprising an antibody or antigen binding fragment thereof which binds to an APC surface molecule selected from the group consisting of CD205 (DEC205), CD204, CD 14, CD206, TLR, Langerin (CD207), DC-SIGN (CD209), CD32, CD68, CD83, CD33, CD54, BDCA-2, BDCA-3, BDCA-4 wherein the antibody or binding fragment thereof fused to a human Notch ligand selected from the group consisting of human Delta1 comprising the amino acid sequence of SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, a human Notch ligand fragment selected from the group consisting of the amino acid sequence of SEQ ID NO: 25, SEQ ID NO: 29, SEQ ID NO: 32, SEQ ID NO: 36, SEQ ID NO: 38 and SEQ ID NO: 39 wherein the fragment retains Notch signaling activity; (3) a composition comprising the conjugate or fusion protein mentioned above and a pharmaceutically acceptable excipient, diluent, or carrier, and (4) a fusion protein prepared by (a) transforming a host cell with an expression vector comprising a polynucleotide sequence encoding the fusion protein mentioned above and (b) culturing the host cell under conditions which provide for expression of said fusion protein, **does not** reasonably provide enablement for any conjugate or fusion protein as set forth in claims 1-2, 8, 29, and 31. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8

USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claims 1-2 encompass any conjugate or fusion protein comprising a first sequence and a second sequence wherein the first sequence *comprises* any antibody or antibody fragment which binds to any antigen presenting cell (APC), and wherein the second sequence *comprises* any Notch ligand DSL domain and at least one EGF-like repeat wherein the second sequence retains Notch signaling activity.

Claim 8 encompasses any conjugate or fusion protein comprising a first sequence and a second sequence wherein the first sequence *comprises* any antibody or antibody fragment which binds to any antigen presenting cell (APC), and wherein the second sequence *comprises* any Notch ligand DSL domain and at least one EGF-like repeat from any Delta, any Jagged, or any Serrate wherein the second sequence retains Notch signaling activity.

Claim 29 encompasses any conjugate prepared by transforming a host with any expression vector comprising any polynucleotide sequence encoding any conjugate comprising any first sequence and any second sequence wherein the first sequence *comprises* any antibody or antibody fragment which binds to any antigen presenting cell (APC), and wherein the second sequence *comprises* any Notch ligand DSL domain and at least one EGF-like repeat wherein the second sequence retains Notch signaling activity.

Claim 31 encompasses any and all composition comprising any conjugate or fusion protein comprising a first sequence and a second sequence wherein the first sequence *comprises* any antibody or antibody fragment which binds to any antigen presenting cell (APC), and wherein the second sequence *comprises* any Notch ligand DSL domain and at least one EGF-like repeat wherein the second sequence retains Notch signaling activity.

The only disclosed use of any conjugate mentioned above is for modulating, i.e., inhibiting or stimulating any T cell signaling pathways, upregulating expression of any Notch, upregulating any activity of any Notch signaling pathway, upregulating expression of any Notch

ligand, upregulating any activity of any Notch ligand or and downstream component of any Notch signaling pathway for treating any diseases (see specification pages 30-34).

The specification discloses only a conjugate comprising a MHC class II binding domain of superantigen TSST1 consisting of SEQ ID NO: 45 as shown at page 41 or Figure 7 conjugated to a Notch ligand Jagged 1 as disclosed on page 66-67 wherein the superantigen TSST1 binds to major histocomplex class II antigen expressed on antigen presenting cell (APC) and wherein the Notch ligand binds to Notch. However, none of the conjugate or fusion protein has been demonstrate to have any biological activity. There is a lack of *in vivo* working examples demonstrating that any conjugate or fusion protein mentioned above when binds to MHC class II molecule expressed on APC and any Notch receptor on T cells upregulates which Notch receptor expression, or upregulates which activity of which Notch receptor, or affecting which downstream component of Notch signaling pathway. Let alone treating any diseases. The specification further discloses the first sequence may be an antibody or binding fragment thereof which binds to an APC surface molecule selected from the group consisting of CD205 (DEC205), CD204, CD 14, CD206, TLR, Langerin (CD207), DC-SIGN (CD209), CD32, CD68, CD83, CD33, CD54, BDCA-2, BDCA-3, BDCA-4 linked to human Delta 1 for targeting population of APCs.

Enablement is not commensurate with how to make and use any conjugate or fusion protein mentioned above comprising any first sequence comprises any antibody or any antibody fragment which binds to any antigen presenting cells (APC) wherein the second sequence comprises any fragment of any Notch ligand that comprises any Notch ligand DSL domain and at least one EGF-like repeat wherein the second sequence retains Notch signaling activity.

This is because "a first sequence comprising any antibody or any antibody fragment that binds to any APC" and second sequence such as any Notch ligand fragment that retains Notch signaling activity without the amino acid sequence has no structure, much less function. The specification as filed does not teach which "fragment of which Notch Ligand" retains Notch signaling activity other than the specific fragment recited in claim 36. The specification does not teach how to make and use any Notch ligand fragment that retains which Notch ligand signaling transduction activity in T cells. There is a lack of guidance as to which amino acids within the full-length sequence of which Notch ligand to be substituted, deleted, added and/or combination thereof such that the Notch ligand still maintains its structure and retains which activity when binds to which Notch receptor, in turn, signaling by modulating, i.e. inhibiting or stimulating

which T cell signaling pathway. Further, the term "comprises" is open-ended. It expands the Notch ligand fragment to include additional amino acids at either or both ends. There is a lack of guidance as to which amino acids to be added and still retain Notch signaling activity.

The Notch signaling in T cell function has a tremendous number of both upstream and downstream effector molecules. The state of the art as summarized by Tsukumo et al (J Immunology 173: 7109-7113, 2004; PTO 892) is such that there are conflicting evidence for Notch signaling on mature T cell activation and differentiation (see abstract, page 7112, in particular). In mammals, there are four Notch receptors (Notch 1-4) and at least five Notch ligands (Jagged 1 and 2, Delta1, 3 and 4) are identified (see page 7109, col. 2, in particular). However, the detailed relationship between Notch signaling and T cells activation/differentiation has not been established (see page 7112, col. 1, in particular). The receptors and ligands can interact with each and the expression pattern of each molecule is not restricted, which makes it difficult to analyze the role of Notch systems in mature T cell differentiation/activation and how T cells utilize different Notch molecules to regulate their own differentiation. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

With regard to antibody or antibody fragment that binds to any APC, there is a lack of specific guidance as to the binding specificity of any and all antibody or antibody fragment since the surface molecule that expressed on which antigen presenting cells, i.e., macrophage, or follicular dendritic cells to which the antibody or antibody fragment binds is not recited in the claims. Until the surface molecule on APC has been identified, the antibody or binding fragment that binds to such surface molecule then can be made using such molecule as an antigen. Given the unlimited number of antibody or antibody fragment, the insufficient guidance as to the antigens or molecules on the surface of antigen presenting cell other than the specific ones recited in claim 35 to be used for making the antibody or binding fragment, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of

the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed October 16, 2008 and January 16, 2008 have been fully considered but they are not persuasive.

Applicants' position is that one of skill in the art would know how to obtain antibodies or antibody fragment against a predetermined antigen.

In response, other than the antibody or antigen binding fragment thereof that binds to antibodies to CD205 (DEC205), CD204, CD14, CD206, TLRs, Langerin (CD207), DC-SIGN (CD209), CD32, CD68, CD83, CD33, CD54 or BDCA-2,3,4, one of skill in the art cannot predict which antibody or antibody fragment conjugated to a second sequence *comprises* any Notch ligand DSL domain and at least one EGF-like repeat wherein the second sequence retains Notch signaling activity still target to antigen presenting cell for treating which disease.

There is a lack of specific guidance as to the binding specificity of any and all antibody or antibody fragment since the surface molecule that expressed on which antigen presenting cells, i.e., macrophage, or follicular dendritic cells to which the antibody or antibody fragment binds is not recited in the claims. Until the surface molecule on APC has been identified, the antibody or binding fragment that binds to such surface molecule then can be made using such molecule as an antigen. Given the unlimited number of antibody or antibody fragment, the insufficient guidance as to the antigens or molecules on the surface of antigen presenting cell other than the specific ones recited in claim35 to be used for making the antibody or binding fragment, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

With regard to a second sequence comprises any Notch ligand fragment comprises any Notch ligand DSL domain and at least one EGF-like repeat wherein the second sequence retains signaling activity, there is insufficient guidance as to which Notch ligand is part of the second sequence. Further, the term "comprises" is open-ended. It expands the Notch ligand fragment to include additional amino acids at either or both ends. There is a lack of specific guidance as to which amino acids to be added and still retain Notch signaling activity.

The Notch signaling in T cell function has a tremendous number of both upstream and downstream effector molecules. The state of the art as summarized by Tsukumo et al (J Immunology 173: 7109-7113, 2004; PTO 892) is such that there are conflicting evidence for Notch signaling on mature T cell activation and differentiation (see abstract, page 7112, in

particular). In mammals, there are four Notch receptors (Notch 1-4) and at least five Notch ligands (Jagged 1 and 2, Delta1, 3 and 4) are identified (see page 7109, col. 2, in particular). However, the detailed relationship between Notch signaling and T cells activation/differentiation has not been established (see page 7112, col. 1, in particular). The receptors and ligands can interact with each and the expression pattern of each molecule is not restricted, which makes it difficult to analyze the role of Notch systems in mature T cell differentiation/activation and how T cells utilize different Notch molecules to regulate their own differentiation. Thus the structure of such sequence in the claimed conjugate and the binding specificity of such conjugate or fusion protein cannot be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention. Thus the structure of such sequence in the claimed conjugate cannot be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

8. Claims 1-2, 8, 29, and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any conjugate or fusion protein as set forth in claims 1-2, 8, 29, and 31.

Claims 1-2 encompass any conjugate or fusion protein comprising a first sequence and a second sequence wherein the first sequence *comprises* any antibody or antibody fragment which binds to any antigen presenting cell (APC), and wherein the second sequence *comprises* any Notch ligand DSL domain and at least one EGF-like repeat wherein the second sequence retains Notch signaling activity.

Claim 8 encompasses any conjugate or fusion protein comprising a first sequence and a second sequence wherein the first sequence *comprises* any antibody or antibody fragment which binds to any antigen presenting cell (APC), and wherein the second sequence *comprises* any Notch ligand DSL domain and at least one EGF-like repeat from any Delta, any Jagged, or any Serrate wherein the second sequence retains Notch signaling activity.

Claim 29 encompasses any conjugate prepared by transforming a host with any expression vector comprising any polynucleotide sequence encoding any conjugate comprising any first sequence and any second sequence wherein the first sequence *comprises* any antibody or antibody fragment which binds to any antigen presenting cell (APC), and wherein the second sequence *comprises* any Notch ligand DSL domain and at least one EGF-like repeat wherein the second sequence retains Notch signaling activity.

Claim 31 encompasses any and all composition comprising any conjugate or fusion protein comprising a first sequence and a second sequence wherein the first sequence *comprises* any antibody or antibody fragment which binds to any antigen presenting cell (APC), and wherein the second sequence *comprises* any Notch ligand DSL domain and at least one EGF-like repeat wherein the second sequence retains Notch signaling activity.

The specification discloses only a conjugate comprising a MHC class II binding domain of superantigen TSST1 consisting of SEQ ID NO: 45 as shown at page 41 or Figure 7 conjugated to a Notch ligand Jagged 1 as disclosed on page 66-67 wherein the superantigen TSST1 binds to major histocomplex class II antigen expressed on antigen presenting cell (APC) and wherein the Notch ligand binds to Notch. However, none of the conjugate or fusion protein has been demonstrate to have any biological activity. There is a lack of in vivo working examples demonstrating that any conjugate or fusion protein mentioned above when binds to MHC class II molecule expressed on APC and any Notch receptor on T cells upregulates which Notch receptor expression, or upregulates which activity of which Notch receptor, or affecting which downstream component of Notch signaling pathway. Let alone treating any diseases. The specification further discloses the first sequence may be an antibody or binding fragment thereof which binds to an APC surface molecule selected from the group consisting of CD205 (DEC205), CD204, CD 14, CD206, TLR, Langerin (CD207), DC-SIGN (CD209), CD32, CD68, CD83, CD33, CD54, BDCA-2, BDCA-3, BDCA-4 linked to human Delta 1 for targeting population of APCs.

At the of filing, applicants are not in possession of any "first sequence comprising any antibody or any antibody fragment that binds to any APC" and second sequence such as any Notch ligand fragment comprises a DSL domain and one or more EGF-like repeat wherein the second sequence retains Notch signaling activity without the amino acid sequence.

The specification as filed does not describe which "fragment of which Notch Ligand" retains Notch signaling activity. The specification does not teach how to make and use any Notch

ligand fragment that retains which Notch ligand signaling transduction activity in T cells. There is a lack of guidance as to which amino acids within the full-length sequence of which Notch ligand to be substituted, deleted, added and/or combination thereof such that the Notch ligand still maintains its structure and retains which activity when binds to which Notch receptor, in turn, signaling by modulating, i.e. inhibiting or stimulating which T cell signaling pathway. Further, the term "comprises" is open-ended. It expands the Notch ligand fragment to include additional amino acids at either or both ends. There is a lack of guidance as to which amino acids to be added and still retain Notch signaling activity.

The Notch signaling in T cell function has a tremendous number of both upstream and downstream effector molecules. The state of the art as summarized by Tsukumo et al (J Immunology 173: 7109-7113, 2004; PTO 892) is such that there are conflicting evidence for Notch signaling on mature T cell activation and differentiation (see abstract, page 7112, in particular). In mammals, there are four Notch receptors (Notch 1-4) and at least five Notch ligands (Jagged 1 and 2, Delta1, 3 and 4) are identified (see page 7109, col. 2, in particular). However, the detailed relationship between Notch signaling and T cells activation/differentiation has not been established (see page 7112, col. 1, in particular). The receptors and ligands can interact with each and the expression pattern of each molecule is not restricted, which makes it difficult to analyze the role of Notch systems in mature T cell differentiation/activation and how T cells utilize different Notch molecules to regulate their own differentiation. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

With regard to antibody or antibody fragment that binds to any APC, there is insufficient disclosure about the binding specificity of any and all antibody or antibody fragment since the surface molecule that expressed on which antigen presenting cells, i.e., macrophage, or follicular dendritic cells to which the antibody or antibody fragment binds is not recited in the claims.

Until the surface molecule on APC has been identified, the antibody or binding fragment thereof that binds to such surface molecule then can be made using such molecule as an antigen. Given the unlimited number of antibody or antibody fragment, the insufficient guidance as to the antigens or molecules on the surface of antigen presenting cell other than the specific ones recited in claim 35 to be used for making the antibody or binding fragment, it would require undue experimentation of one skilled in the art to practice the claimed invention. Thus the structure of

the claimed conjugate as a whole cannot be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

The specification discloses only one conjugate comprising only human Notch ligand fused to TSST-1 that binds to MHC class II, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of conjugate or fusion protein to describe the genus for the claimed conjugate comprising any antibody or antibody fragment which binds to any antigen presenting cell (APC) and any second sequence comprises any Notch ligand or any fragment thereof comprising a Notch ligand DSL domain and one or more EGF-like repeat. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed October 16, 2008 and January 16, 2008 have been fully considered but they are not persuasive.

Applicants' position is that one of skill in the art would know how to obtain antibodies or antibody fragment against a predetermined antigen. The second sequence of the instant invention is directed to a Notch ligand DSL domain and at least one EGF-like repeat, and there is sufficient guidance in the specification and figures, and knowledge in the field at the time the application was filed, to enable the invention as claimed. For example, the specification discloses that Notch ligands display multiple EGF-like repeats and a DSL domain (page 43, lines 20-31, and Figures 2 and 3), and lists examples of mammalian Notch ligands identified at the time the application was filed (page 9, lines 19-28). Knowledge in the field at the time of filing also confirms the specification's disclosure that Notch ligands display multiple EGF-like repeats and a DSL domain (Artavantis-Tsakonas, *et al.* Science 284: 770-776, 1999).

The specification further notes that "homology between [Notch ligand] family members is extensive" (page 9, line 27), which thereby suggests that one skilled in the art can apply the guidance provided by the specification to easily obtain the Notch ligands encompassed by the scope of the instant claims. Applicants' arguments are further supported by Figure 8, which shows schematic representations of the Notch ligands Jagged and Delta and confirms the

presence of a DSL domain and at least one EGF-like repeat in these ligands, and Figure 9, which shows aligned amino acid sequences of DSL domains from various Drosophila and mammalian Notch ligands and confirms that a DSL domain and at least one EGF-like repeat is widely present. Therefore, based on the teachings of the specification and figures, and in consideration of what was known in the art at the time the present application was filed, one skilled in the art would not require undue experimentation to obtain a sequence comprising a Notch ligand DSL domain and at least one EGF-like repeat while retaining Notch signaling activity.

In response, at the of filing, applicants are not in possession of any "first sequence comprising any antibody or any antibody fragment that binds to any APC" and second sequence such as any Notch ligand fragment comprises a DSL domain and one or more EGF-like repeat wherein the second sequence retains Notch signaling activity without the amino acid sequence. Other than the antibody or antigen binding fragment thereof that binds to antibodies to an APC surface molecule selected from the group consisting of CD205 (DEC205), CD204, CD14, CD206, TLRs, Langerin (CD207), DC-SIGN (CD209), CD32, CD68, CD83, CD33, CD54 or BDCA-2,3,4, the binding specificity of any and all antibody or antibody fragment in the claimed conjugate is not adequately describe since the surface molecule that expressed on which antigen presenting cells, i.e., macrophage, or follicular dendritic cells is not recited in the claims. One of skill in the art cannot predict which antibody or antibody fragment conjugated to a second sequence *comprises* any Notch ligand DSL domain and at least one EGF-like repeat wherein the second sequence retains Notch signaling activity still target to antigen presenting cell (APC) for treating which disease.

With respect to second sequence *comprises* any Notch ligand DSL domain and at least one EGF-like repeat wherein the second sequence retains Notch signaling activity, the specification as filed does not describe which "fragment of which Notch Ligand" retains Notch signaling activity. The specification does not teach how to make and use any Notch ligand fragment that retains which Notch ligand signaling transduction activity in T cells. There is a lack of guidance as to which amino acids within the full-length sequence of which Notch ligand to be substituted, deleted, added and/or combination thereof such that the Notch ligand still maintains its structure and retains which activity when binds to which Notch receptor, in turn, signaling by modulating, i.e. inhibiting or stimulating which T cell signaling pathway. Further, the term "comprises" is open-ended. It expands the Notch ligand fragment to include additional

amino acids at either or both ends. There is a lack of guidance as to which amino acids to be added and still retain Notch signaling activity.

The Notch signaling in T cell function has a tremendous number of both upstream and downstream effector molecules. The state of the art as summarized by Tsukumo et al (J Immunology 173: 7109-7113, 2004; PTO 892) is such that there are conflicting evidence for Notch signaling on mature T cell activation and differentiation (see abstract, page 7112, in particular). In mammals, there are four Notch receptors (Notch 1-4) and at least five Notch ligands (Jagged 1 and 2, Delta1, 3 and 4) are identified (see page 7109, col. 2, in particular). However, the detailed relationship between Notch signaling and T cells activation/differentiation has not been established (see page 7112, col. 1, in particular). The receptors and ligands can interact with each and the expression pattern of each molecule is not restricted, which makes it difficult to analyze the role of Notch systems in mature T cell differentiation/activation and how T cells utilize different Notch molecules to regulate their own differentiation.

Thus the structure of the claimed conjugate as a whole cannot be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 2 and 29 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "A *conjugate* prepared by *transforming* a host cell…" in claim 29 is ambiguous and indefinite because transforming host cell produces fusion protein, NOT a conjugate. A conjugate involves chemical coupling of two proteins, see specification at page 26, lines 11-27. The specification at page 24-25 discloses the *fusion polypeptide* or fusion protein is produced by transforming host cell with an expression vector comprising a polynucleotide encoding the fusion polypeptide to produce the fusion protein. It is suggested that claim 2 be rewritten as an independent claim starting with a fusion protein comprising …and claim 29 be depended from claim 2 would obviate this rejection.

Applicants' arguments filed October 16, 2008 and January 16, 2008 have been fully considered but they are not persuasive.

Applicants' position is the specification which recites "conjugates include fusion proteins in which the targeting protein is linked to a protein for T cell signaling modulation" (see page 4, lines 4-17). Therefore, the conjugate of the claimed invention can be a fusion protein and can be prepared by transforming a cell.

In response, the claims as presented are improper. A conjugate is made by chemical conjugation of first sequence to a second sequence. A fusion protein is made by recombinant DNA encoding a fusion protein comprising a first sequence and second sequence by transforming host cell with an expression vector comprising a polynucleotide sequence encoding a fusion protein and culturing the host cell under conditions which express the fusion protein. Neither the art nor the specification teaches a conjugate can be prepared by transforming a host cell as recited in claim 29.

It is suggested that claim 2 be rewritten as an independent claim starting with "A fusion protein comprising a first sequence and a second sequence…signaling activity" would obviated this rejection.

It is further suggested that claim 29 be depended from claim 2 would obviate this rejection.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-2, 8, 29, 31 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/20142 publication (of record, published May 14, 1998; PTO 1449).

The WO 98/20142 publication teaches a protein comprising a first sequence operably linked to a second sequence wherein the first sequence is an antibody fragment such as human IgG1-Fc that binds to an antigen presenting cell (APC) and a second sequence such as the extracellular domain of Notch ligand selected from Delta or Serrate or fragments or derivatives or analogs thereof (see claims 4-6, 15-17 of the WO 98/20142 publication, pages 8 and 16, in particular). The reference antibody Fc fragment inherently binds to the APC cell surface

molecule such as the CD32 receptor on antigen presenting cell, which is the low affinity Fcγ receptor. The reference extracellular domain of Notch ligand fusion protein retains the ability to bind to Notch and inhibits its signaling activity since the notch ligand contains DSL domain which is the 20-22 amino acids at the amino terminus of the protein and between 3-8 EGF-like repeats on the extracellular domain (see page 4, lines 20-22, page 2, line 12-14, in particular). The term "at least one" implies one or more EGFR-like repeat. The term "comprises" is open-ended. It expands the fragment of Notch ligand to include additional amino acids at either or both ends to read on the full-length Notch ligand.

The WO 98/20142 publication further teaches a composition comprising the reference fusion protein (see page 11, line 21-26, in particular). The reference protein is produced by transforming a host cell such as *E coli* or COS cell with en expression vector such as pIG-1 comprising the nucleic acid encoding the reference fusion protein and culturing the host cell under conditions to produce the reference protein (see page 16, Example 2, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed October 16, 2008 and January 16, 2008 have been fully considered but are not found persuasive.

Applicants' position is that claims 1, 8 and 35 have been amended to recite the first sequence comprises an antibody or antibody fragment which binds to an antigen presenting cell (APC). In WO 98/20142 there is no specific and unambiguous disclosure of a conjugate comprising a first sequence comprising an antibody or fragment thereof which binds to an APC. Thus, the present invention is distinguished over WO 98/20142.

In response, the WO 98/20142 publication teaches a protein comprising a first sequence operably linked to a second sequence wherein the first sequence is an *antibody fragment* such as human IgG1-Fc that binds to an antigen presenting cell (APC) and a second sequence such as the extracellular domain of Notch ligand selected from Delta or Serrate or fragments or derivatives or analogs thereof (see claims 4-6, 15-17 of the WO 98/20142 publication, pages 8 and 16, in particular).

13. The following new grounds of objection and rejections are necessitated by the amendment filed October 16, 2008 and January 16, 2008.

14. The word "signalling" in claim 1 is misspelled.

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claim 35 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. **This is New Matter**.

The recitation of "an antibody or antibody fragment which binds to an APC surface molecule wherein the APC surface molecule is an *MHC class II* molecule" in the amended claim 35 represents a departure from the specification and claims as originally filed.

The specification discloses only superantigen, NOT antibody or antibody fragment, is capable of binding to an MHC class II molecule on APC, see page 39, and pages 12-13.

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

18. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

19. Claims 1-2, 8, 29, 31 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0861894 B1 (newly cited published Sept 2, 1998; PTO 892).

Claim 1 is interpreted as a fusion protein as evidenced by claims 2 and 29 as well as the specification which discloses "conjugates include fusion proteins in which the targeting protein is linked to a protein for T cell signaling modulation" (see page 4, lines 4-17).

The EP 0861894 B1 patent teaches a chimeric fusion protein comprising a first sequence linked to a second sequence wherein the first sequence is an antibody fragment such as human IgG Fc which inherently binds to an antigen presenting cell (APC) via CD32 receptor expressed on APC and a second sequence comprises a Notch ligand such as human Delta-1 comprising a Notch ligand DSL domain and at least one EGF-like repeat (see page 16, line 1-24, page 10, line 4-6, page 7, line 5-18, in particular). The EP 0861894 A1 patent also teaches a chimeric fusion protein comprising a first sequence and a second sequence wherein the first sequence is an antibody fragment such as human IgG Fc which inherently binds to an antigen presenting cell (APC) via CD32 receptor expressed on APC and a second sequence comprises a Notch ligand such as human Serrate-1 consists of 1218 amino acids residues identical to the claimed SEQ ID NO: 43 (see page 7, line 25-26, reference SEQ ID NO: 9, page 10, line 27-28, page 17, line 34, in particular). The reference fusion protein is prepared by transforming host cell such as COS-7 cells with a vector comprising nucleic acid encoding the reference chimeric fusion protein (see page 16 through 19, page 8, lines 25-27, in particular). The EP 0861894 A1 patent teaches a composition comprising the reference chimeric fusion protein and a pharmaceutically acceptable carrier such as distilled water for injection (see page 10, line 52-54, in particular). Thus, the reference teachings anticipate the claimed invention.

20. Claims 1-2, 8, 29, 31 and 36 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,664,098 B1 (newly cited, filed Dec 30, 1999; PTO 892).

Claim 1 is interpreted as a fusion protein as evidenced by claims 2 and 29 as well as the specification which discloses "conjugates include fusion proteins in which the targeting protein is linked to a protein for T cell signaling modulation" (see page 4, lines 4-17).

The '098 patent teaches chimeric fusion protein comprising Notch ligand such as a human Delta2 polypeptide comprising the amino acid sequence that is 100 % identical to the claimed SEQ ID NO: 42 fused to an antibody fragment such as human IgG Fc (see reference SEQ ID NO: 25, col. 11, line 57-62, col. 12, line 63-65, in particular). The reference Notch ligand

comprises DSL sequence and repeated EGF-like sequence (see col. 8, line 49-60, in particular). The reference human Delta-2 is useful for proliferation of undifferentiated blood cells and inhibition of differentiation, see abstract, in particular. The reference fusion protein is prepared by transforming host cell such as COS-7 cells with a vector comprising nucleic acid encoding the reference chimeric fusion protein (see col. 11, line 19-40, in particular). The patent teaches a composition comprising the reference chimeric fusion protein and a pharmaceutically acceptable carrier such as distilled water for injection (see paragraph bridging col. 31 and 32, in particular). Thus, the reference teachings anticipate the claimed invention.

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 1 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/20142 publication (of record, published May 14, 1998; PTO 1449) in view of Snider et al (newly cited, J Immunology 139: 1609-1616, Sept 1987; PTO 892), US 20030148316 application (newly cited, claimed earliest priority to provisional application filed August 1, 2001; PTO 892), Wollenberg et al (newly cited, J Invest Dermatol 118: 327-334, 2002; PTO 892), and/or Noorman et al (newly cited, J Leukocyte Biology 61: 63-72, 1997; PTO 892).

The teachings of the WO 98/20142 publication have been discussed supra. The WO 98/20142 publication teaches the Notch ligand fusion protein is useful for mediating Notch

signaling activity by induction of tolerance for treating allergy, asthma, and infectious disease (see abstract, in particular).

The invention in claim 35 differs from the teachings of the reference only in that the conjugate wherein the first sequence is an antibody or antibody fragment which binds to an APC surface molecule wherein the APC surface molecule is an CD206 (mannose receptor) instead of the antibody Fc fragment.

Snider et al teach a method of targeting antigen to antigen presenting cell (APC) using antigen conjugated antibody that binds to a protein antigen or cell marker such as MHC class II or Fc gamma receptor expressed on antigen presenting cell (APC), see entire document, abstract, page 1609, col. 2, second paragraph, in particular. The advantages are less antigen is required and the antigen presentation is enhanced only when the antibodies were covalently crosslinked or conjugated to the antigen such as OVA, see page 1610, col. 2, last paragraph, in particular.

The US 20030148316 application teaches various cell surface marker such as mannose receptor CD206 expressed on antigen presenting cell such as macrophage after exposure to CpG (see page 17, Table 5b, in particular).

Wollenberg et al teach mannose receptor 206 is expressed on inflammatory antigen presenting cell such as epidermal dendritic cells and can be detected by monoclonal antibody D547 (see abstract, page 328, col. 1, Materials and methods, in particular).

Noorman et al teach various monoclonal antibodies such as mAb 15-2 against human mannose receptor as a specific marker for antigen presenting cell such as macrophages and monocytes (see abstract, in particular). Noorman et al further teach commonly used specific marker for human macrophages includes CD14, CD68, see page 63, col. 2, first full paragraph, in particular.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody Fc fragment in the fusion protein comprising a Notch ligand or fragment thereof comprising DSL domain and EGF-like repeats retains Notch signaling activity as taught by the WO 98/20142 publication for the antibody that binds to any antigen presenting cell surface molecule such as MHC class II as taught by Snider, or the antibody that binds to mannose receptor as taught by US 20030148316 application and Wollenberg et al or Noorman et al.

Alternatively, it would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate any Notch ligand or fragment thereof comprising DSL domain and EGF-like repeats retains Notch signaling activity as taught by the WO 98/20142 publication to any antibody that binds to any antigen presenting cell surface molecule such as MHC class II as taught by Snider, or to the antibody that binds to mannose receptor as taught by US 20030148316 application and Wollenberg et al or Noorman et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with the expectation of success to do this because Snider et al teach the advantages of targeting antigen presenting using antibody is that less antigen is required and the antigen presentation is enhanced only when the antibodies were covalently crosslinked or conjugated to the antigen such as OVA, see page 1610, col. 2, last paragraph, in particular.

One having ordinary skill in the art would have been motivated with the expectation of success to substitute one antibody for another because Noorman et al teach monoclonal antibody such as mAb 15-2 binds to human mannose receptor and is a specific marker for antigen presenting cell such as macrophages and monocytes (see abstract, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to substitute one antibody for another because Wollenberg et al teach mannose receptor 206 is expressed on antigen presenting cell such as inflammatory epidermal dendritic cells and can be detected by monoclonal antibody D547 (see abstract, page 328, col. 1, Materials and methods, in particular).

24. Claims 1 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/20142 publication (of record, published May 14, 1998; PTO 1449) in view of Snider et al (J Immunology 139: 1609-1616, Sept 1987; PTO 892), US 20030148316 application (newly cited, claimed earliest priority to provisional application filed August 1, 2001; PTO 892), Wollenberg et al (newly cited, J Invest Dermatol 118: 327-334, 2002; PTO 892), and/or Noorman et al (newly cited, J Leukocyte Biology 61: 63-72, 1997; PTO 892) as applied to claims 1 and 35 and further in view of US Pat No 6,664,098 B1 (newly cited, filed Dec 30, 1999; PTO 892) or US Pat No 6,136,952 (newly cited, Oct 24, 2000; PTO 892).

The combined teachings of the WO 98/20142 publication, Snider et al, US 20030148316 application, Wollenberg et al, and/or Noorman et al have been discussed supra.

The invention in claim and 36 differs from the teachings of the references only in that the conjugate wherein the second sequence is human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42 or human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43.

The '098 patent teaches Notch ligand such as a human Delta2 polypeptide comprising the amino acid sequence that is 100 % identical to the claimed SEQ ID NO: 42 (see reference SEQ ID NO: 25, in particular). The reference Notch ligand comprises DSL sequence and repeated EGF-like sequence (see col. 8, line 49-60, in particular). Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The reference human Delta-2 is useful for proliferation of undifferentiated blood cells and inhibition of differentiation, see abstract, in particular.

The '952 patent teaches Notch ligand such as human JAGGED comprising the amino acid sequence of SEQ ID NO: 2, which is 100% identical to the claimed SEQ ID NO: 43, see reference SEQ ID NO: 2, col. 7, line 65-66, in particular. The reference JAGGED includes a DSL domain and tandem epidermal growth factor repeat (see col. 5, lines 27-33, in particular). Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The reference ligand is useful for inhibiting hematopoietic cell differentiation (see col. 16, line 42-60, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the Notch ligand in the conjugate of WO 98/20142 publication, Snider et al, US 20030148316 application, Wollenberg et al, and/or Noorman et al for the Notch ligand such as such as a human Delta2 as taught by the '098 patent or the Notch ligand such as human JAGGED-1 or 2 as taught by the '952 patent.

One having ordinary skill in the art would have been motivated with the expectation of success to substitute because the '098 patent teaches the reference human Delta-2 is useful for proliferation of undifferentiated blood cells and inhibition of differentiation, see abstract, in particular.

One having ordinary skill in the art would have been motivated with the expectation of success to substitute because the '952 patent teaches human JAGGED is useful for inhibiting hematopoietic cell differentiation (see col. 16, line 42-60, in particular).

25. SEQ ID NO: 25, 29, 32, 36, 39, 40 and 44 are free of prior art.

26. No claim is allowed.

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

29. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
January 2, 2009